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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	21

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,320	PELED ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 37-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 37-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment, filed 12/04/02 (Paper No. 20), is acknowledged.

Claims 1-15 and 37-47 are pending.

Applicant's election of neonatal umbilical cord blood as species of specific hematopoietic cells , tetraethylenepentamine (TEPA) as specific transition metal chelator, stem cell factor and GM-CSF as specific early and late acting cytokine in Paper No. 20 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is notes however, that only claims 1-15 but not claims 37-47 were amended to read on the elected species.

Claims 1-15 and 37-47, as they all read on the elected species wherein neonatal umbilical cord blood is species of specific hematopoietic cells , tetraethylenepentamine (TEPA) is specific transition metal chelator, stem cell factor and GM-CSF is specific early and late acting cytokine are under consideration in the instant application.

2. The instant claims may not have the benefit under 35 U.S.C. § 120 of all of the parent filing dates. The subject matter claimed in Claims 3-5, 7, 39, and 45 , that is a method of hematopoietic cells transplantation, wherein hematopoietic cells are obtained from neonatal umbilical cord blood and wherein transition metal chelator is tetraethylenepentamine dose not have a support in the parent applications Serial Numbers: 09/161/695, 09/130,367 and 09/024195.

If applicants disagree, applicants should present a detailed analysis as to why the claimed subject matter has clear support in the parent applications.

The specification on page 1, line 15 should be amended to reflect the status of the parent applications 09/161,695, 09/130,367 and 09/024,195.

3. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Applicant is reminded that changes in the Brief Description of the Drawings will be required in accordance with these changes.

4. Claims 1-15 and 37-47 are objected to because of the following informalities: The word "copper" is misspelled in claims 1 and 37. Appropriate correction is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 and 37-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of hematopoietic cells transplantation and a method of adoptive immunotherapy, comprising a step of providing CD4+ ex-vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population of said cells, while at the same time inhibiting differentiation of said cells does not reasonably provide **enablement** for a method of hematopoietic cells transplantation and a method of adoptive immunotherapy, comprising a step of providing *any* cells ex-vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population of said cells, while at the same time inhibiting differentiation of said cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses that providing $CD4^+$ cells *ex-vivo* with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, only $CD4^+$ cells expanding and at the same time inhibiting differentiation (see examples 1 and 2 in particular).

The specification does not adequately teach how to effectively expand and at the same time inhibit differentiation of *any* cells by providing said cells ex-vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper.

The specification does not teach how to extrapolate data obtained from $CD4^+$ cells *ex-vivo* assay studies to the development of effective protocols for imposing proliferation and at the same time restricting differentiation of *any* stem or progenitor cells by culturing said cells under conditions that reduces the capacity of said cells in utilizing copper. Moreover, Applicant himself acknowledge that the mechanism of the effects of cupper is unknown (see page 3, line 35-37 in particular). As such, the invention must be considered unpredictable. In addition,

Percival (Am .J. Clin. Nutr. 1998, Vol.67 p.1064-1068) teaches that the role of copper in effecting cellular function is contradictory and that more studies have to be done to understand the mechanisms by which copper effect the process of differentiation in various types of cells (see entire document, pages 1064 and 1066 in particular).

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of hematopoietic cells transplantation and a method of adoptive immunotherapy, comprising a step of providing *any* cells ex-vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population of said cells, while at the same time inhibiting differentiation of said cells. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-5, 8-15, 37 and 40-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al(Blood Cells, 1994, v.20, pages 468-481) or C.De Bruyn et al., (Stem Cells 1995, v.13, pages 281-288) each in view of Cicuttine et al (Blood, 1992, v 80, pp 102-112).

Moore et al. teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient (see, entire document, abstract in particular). Moore et al. teach that the hematopoietic stem cells can be derived from umbilical cord blood (see page 469 in particular). Moore et al. teach a growth medium with nutrients and early and late acting cytokines (See Material and Methods in particular). Moore et al. teach that ex vivo expansion of cord blood CD34+/CD38- cells will permit improved engraftment of adults (see abstract in particular).

Similarly, C.De Bruyn et al. teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining $CD34^+$ hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient (see, entire document, abstract in particular) C.De Bruyn et al. teach that the hematopoietic stem cells can be derived from umbilical cord blood or from bone marrow (see Page 282, in particular). Moore et al. teach a growth medium with nutrients and early and late acting cytokines (See Material and Methods in particular).

Moore et al. or C.De Bruyn et al. does not explicitly teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, under define growth conditions for reducing a capacity of hematopoietic cells in utilizing copper that will stimulate growth while inhibit differentiation .

Cicuttine et al. teach a method of culturing hematopietic progenitor cells using define growth condition that will stimulate growth while inhibit differentiation (see entire document, page 104, column 2 in particular). The growth media containing nutrients, early and late acting cytokines and zinc. As taught by Cicuttine et al. (see Discussion in particular) zinc has an affinity to copper and thus would reduce copper utilization of culturing hematopoietic cells. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made that culturing the cell in the medium containing zinc would reduce a capacity of hematopoietic cells in utilizing cooper, absent a showing of unobvious property.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Cicuttine et al. to those of Moore et al. or C.De Bruyn et al. to obtain a claimed method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising the steps of culturing cells ex vivo under define growth conditions for reducing a capacity of hematopoietic cells in utilizing copper, using media containing zinc, which will reduce a capacity of culturing cells in utilizing copper, thereby stimulate cell proliferation while inhibiting differentiation of said cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because cultivating cells under growth conditions for reducing a capacity in utilizing copper using zinc containing medium will support only growth, proliferation and expansion without inducing differentiation of said cells as taught by Cicuttine et al. that can be further used a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient as taught by Moore et al. or C.De Bruyn et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. Claims 6-7 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al(Blood Cells, 1994, v.20, pages 468-481) or C.De Bruyn et al., (Stem Cells 1995, v.13, pages 281-288) each in view of Percival et al (J Nutrition, 1922, v122 pages 2424-2429)

The teaching of Moore et al. and C.De Bruyn et al. have been discussed, supra.

Moore et al. or C.De Bruyn et al. does not explicitly teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, under define growth conditions for reducing a capacity of hematopoietic cells in utilizing cooper, using a tetraethylenepentamine as a transition metal chelator.

Percival et al. teach culturing condition using define growth medium condition that will stimulate growth while inhibit differentiation. (see entire document, Abstract in particular). Percival et al. teach that cells can be made copper deficient by incubating them in the media containing tetraethylenepentamine (see Material and Methods in particular). Percival et al. teach that copper is essential for the process of differentiation and chelating cooper with tetraethylenepentamine will inhibit differentiation (see page 2428 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Percival et al. to those of Moore et al. or C.De Bruyn et al. to obtain a claimed method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising the steps of culturing cells ex vivo under define growth conditions for reducing a capacity of hematopoietic cells in utilizing copper, using a tetraethylenepentamine as a transition metal chelator, thereby stimulate cell proliferation while inhibiting differentiation of said cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because cultivating cells under growth conditions for reducing a capacity in utilizing cooper using a tetraethylenepentamine as a transition metal chelator, will support only growth, proliferation and expansion without inducing differentiation of said cells as taught by Percival et al., that can be further used a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient as taught by Moore et al. or C.De Bruyn et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. No claim is allowed.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
February 10, 2003.

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